

SEQ ID N :17, or an N-terminal fragment thereof having a molecular weight of about 19 kD, which *hedgehog* amino acid sequence or fragment thereof binds to a *patched* protein or regulates proliferation of testicular germ line cells.

75. (New) An isolated nucleic acid encoding a polypeptide consisting of a *hedgehog* amino acid sequence which is at least 98 percent identical to a *hedgehog* protein of SEQ ID No:17, or an N-terminal fragment thereof having a molecular weight of about 19 kD, which *hedgehog* amino acid sequence or fragment thereof binds to a *patched* protein or regulates proliferation of testicular germ line cells.

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REMARKS

Claims 35, 39, 40, 42, 43, 49, 52-54, 62-70, and 72-75 constitute the pending claims in the present application. Applicants submit that added claims 72-75 raise no new issues, and should thus be entered. Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

1. Applicants note that the Art Unit and Examiner for this application have changed.
2. Applicants note that the specification has been amended following the amendments in Paper 29 and the corrections in Paper 30.
- 3-4. Applicants note that claims 1-35, 39-43, 47-49, and 52-71 are pending, and that claims 1-34, 39-43, 47, 48, 55-61, and 71 are withdrawn as being directed to a non-elected invention. Applicants will cancel such claims upon indication of allowable subject matter.
5. Applicants note with appreciation that the application appears to comply with sequence listing requirements.
6. Applicants note with appreciation the withdrawal of the rejection under 35 U.S.C. 101.
7. Applicants gratefully note the withdrawal of the written description rejection.

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8-10. Applicants note with appreciation the withdrawal of rejections under 35 U.S.C. 102(b).

11. Claims 35, 39, 40, 42, 43, 63, 65, 69, and 70 are rejected under 35 U.S.C. 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Office Action also appears to reject these claims on the basis of insufficient written description as well. Applicants respectfully traverse this rejection(s).

Applicants would first like to point out that the claims recite, as fragments, N-terminal fragments of about 19 kD in size which bind to *patched*. As noted in the application on page 21, line 22, the full-length protein is approximately 46 kD, and thus fragments within the scope of the claim are nearly half the size of the full-length protein, have a specific function, and are taken from a designated portion of the full-length protein. Accordingly, Applicants submit that the number of fragments included within the scope of the claim is not "almost limitless", as suggested by the Office Action.

Additionally, Applicants submit that the present application is rife with written description far more than adequate to support and enable the scope of the pending claims. The Examiners attention is directed to several points in the specification which describe various polypeptide sequences. On page 4, lines 20-21, the specification points out that preferred fragments of *Dhh* include residues 23-198 of SEQ ID No. 17. Applicants point out that a sequence 98% identical to this fragment would include at most four variant amino acids. Even the full length of SEQ ID No. 17, at 396 amino acids, would meet this limitation only with fewer than ten variant amino acids. On page 21, Applicants describe no fewer than ten different *hedgehog* protein sequences. As Applicants have previously pointed out, all of these sequences are highly conserved in the N-terminal portion, which portion is primarily responsible for the biological activity of *hedgehog* proteins. Accordingly, one of skill in the art would recognize that amino acids which differ between the various sequences could be readily interchanged without adversely affecting activity, and that the C-terminal portion of the molecule would be quite receptive to substitution with relative impunity.

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On page 27, Applicants point out various preferred subsequences of the disclosed *hedgehog* proteins. Lines 30-33 point out particular fragments of SEQ ID No. 17. Moreover, Applicants provide additional guidance from page 28, line 32, to page 29, line 16, pointing out conservative substitutions that can be employed to produce variant sequences likely to retain the biological activity of the natural sequence. Exemplary degenerate sequences are also provided in the specification on pages 30-32, as well, and would be useful to the skilled artisan in designing variant sequences that retain the desired biological activity.

Applicants again point out that Chang et al., *Development* 1994, 120, 3339-3353, previously made of record, indicates that Hhg-1, a mouse Sonic hedgehog gene, functions in *Drosophila* in a manner similar to the native *Drosophila* hedgehog protein, as described on pages 3344-3347, despite the fact that these polypeptides are only approximately 46% identical. Accordingly, Applicants submit that one of skill in the art could have readily produced variants of SEQ ID No. 17 or N-terminal fragments thereof using the other known sequences as a guide to which substitutions would be expected to retain activity.

The test for compliance with the written description requirement, as noted in MPEP 2163.02, is "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Stated another way, the test is whether the specification "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 227 USPQ 177, 179 (Fed. Cir. 1985). As these statements clearly suggest, whether or not a specification provides adequate written description for claimed subject matter must be determined in light of the level of skill in the relevant art. *In re Alton*, 37 USPQ2d 1578 (Fed. Cir. 1996), *In re Lange*, 209 USPQ 288 (CCPA 1981).

One of skill in the art reading the specification at the time of filing would have recognized that Applicants were in possession of the full scope of the pending claims, because the specification shows clear recognition of the structure-activity relationship of *hedgehog* proteins and demonstrates considerable understanding of how amino acids can be replaced and fragments selected with an eye towards retaining biological activity. Applicants further submit that the written description is more than sufficient to instruct one of skill in the art how to make

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variant sequences encoding polypeptides which retain the desired biological activity.

Particularly, given that Chang et al. found that Hhg-1 and Drosophila *hedgehog*, though more than 30% divergent in the biologically active N-terminus and more than 50% divergent overall, showed comparable biological activity, the implicit suggestion in the Office Action that replacing 2% of the amino acids of a *Dhh* sequence is likely to destroy biological activity in most cases seems untenable at best. For the reasons set forth above, Applicants submit that the present claims are fully enabled and supported by the specification as filed. Reconsideration and withdrawal of this rejection is respectfully requested.

12. Claims 63 and 67 are rejected under 35 U.S.C. 102(b) as being anticipated by Hillier et al. Applicants respectfully traverse this rejection to the extent it is maintained over the claims as amended.

The Office Action states that "there is no requirement that the reference teach how to use the product." The Examiner's attention is directed to MPEP 2121.01(I). This section states that "a 35 U.S.C. 102 rejection [can be made] even if the reference does not itself teach one of ordinary skill how to... make or use the article disclosed." However, this statement is further clarified, by pointing out that "secondary evidence... can be cited to show public possession of the method of making and/or using." The Examiner has not provided any such evidence demonstrating public possession of the method of using the sequences of Hillier et al.

Nevertheless, Applicants have amended claim 63 to more particularly point out that only nucleic acids encoding naturally occurring *Desert hedgehog* proteins, and that those proteins are not fragments other than the recited fragment of about 19 kD. Accordingly, Applicants submit that these claims are not anticipated by Hillier et al., however applied.

13-14. Applicants have amended claims 43 and 35 as requested by the Examiner.

15. Claims 35, 39, 40, 42, 43, 49, 52-54, and 62 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite. Applicants have amended claims 35 and 49 to overcome the Examiner's rejection. Applicants submit that these amendments do not alter the scope of the claims as previously presented. Reconsideration and withdrawal of this rejection is respectfully requested.

16. Applicants note with appreciation that the subject matter of claims 64, 66, and 68 is found allowable.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at 617-832-1000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this application be charged to **Deposit Account No. 06-1448**.

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Respectfully Submitted,

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